Patterns of chronic hand eczema: a semantic map analysis of the CARPE registry data

Cazzaniga, S ; Apfelbacher, C ; Diepgen, Thomas ; Ofenloch, R F ; Weisshaar, E ; Molin, S ; Bauer, A ; Mahler, Vera ; Elsner, P ; Schmitt, J ; Ballmer-Weber, B K ; Spring, P ; Naldi, L ; Borradori, L ; Simon, D

Abstract: BACKGROUND: Hand eczema has a high incidence and prevalence and has a negative impact on both physical and psychological well-being, with the risk of persistence as a chronic condition. Epidemiological studies on hand eczema provided mainly descriptive and risk analyses, but pattern analyses of variables associated with hand eczema, in particular chronic hand eczema, have not been explored to date. OBJECTIVES: To investigate and display the semantics of associations between variables of hand eczema obtained from the Swiss and German registries of chronic hand eczema (CARPE) to dissect patterns and novel links. METHODS: This was a cross-sectional study on selected variables from the CARPE registries. Associations between variables were analysed by means of an autoassociative system. A semantic connectivity map was generated by using a maximum spanning tree algorithm. RESULTS: Baseline datasets of 1466 patients with chronic hand eczema (Switzerland: 199; Germany: 1267) were analysed. Occupational exposure had the highest impact in the total and country cohorts. We identified two areas of exposure linked to corresponding occupations that clearly demarcated the sexes. CONCLUSIONS: This study, using semantic connectivity as a novel method of data analysis, reveals the complexity of features characterizing chronic hand eczema as well as novel association patterns that deserve further investigation.

DOI: https://doi.org/10.1111/bjd.15660

Patterns of chronic hand eczema: a semantic map analysis of the CARPE registry data

S. Cazzaniga,[1,2] C. Apfelbacher,[3] T. Diepgen,[4] R. Ofenloch,[4] E. Weisshaar,[4] S. Molin,[5] A. Bauer,[6] V. Mahler,[7] P. Elsner,[8] J. Schmitt,[9] B. K. Ballmer-Weber,[10] P. Spring,[11] L. Naldi [2,12], L. Borradori,[1] D. Simon [1]

for the CARPE study groups of Germany and Switzerland

[1]Department of Dermatology, Inselspital, Bern University Hospital, Bern Switzerland

[2]Centro Studi GISED, Bergamo, Italy

[3]Institute of Epidemiology and Preventive Medicine, University of Regensburg, Regensburg, Germany

[4]Department of Clinical Social Medicine, Occupational and Environmental Dermatology, University Hospital, Ruprecht Karls University, Heidelberg, Germany

[5]Department of Dermatology and Allergy, Ludwig Maximilian University, Munich, Germany

[6]Department of Dermatology, University Hospital Carl Gustav Carus, Technical University Dresden, Dresden, Germany

[7]Department of Dermatology, University Hospital of Erlangen, Friedrich Alexander University Erlangen-Nuremberg, Erlangen, Germany

[8]Department of Dermatology and Dermatological Allergy, Friedrich Schiller University Jena, Jena, Germany

[9]Centre for Evidence-based Healthcare, Medical Faculty Carl Gustav Carus, Technical University Dresden, Dresden, Germany

[10]Allergy Unit, Department of Dermatology, University Hospital Zürich, Zurich, Switzerland

[11]Department of Dermatology, University Hospital of Lausanne CHUV, Lausanne, Switzerland

[12]Department of Dermatology, Papa Giovanni XXIII Hospital, Bergamo, Italy.

Correspondence:
Dr. Dagmar Simon, MD
Dept. of Dermatology, Inselspital, 3010 Bern, Switzerland
Tel : +41 31 632 2278
Fax : +41 31 632 2233
e-mail: dagmar.simon@insel.ch

Running head: Patterns of chronic hand eczema

Words: 3063
Tables: 1
Figures: 2
Supporting information: Supplementary Tables: 7
Supplementary Figures: 4

Funding sources: The Carpe registries were supported by research grants from Basilea Pharmaceutica International AG and Glaxo SmithKline AG Switzerland.

Conflict of interest: The authors declare no conflicts of interest.

Bulleted statements

What's already known about this topic?

- Chronic hand eczema is a multifactorial disease.
- Epidemiological studies on hand eczema provide mainly descriptive and risk analyses.

What does this study add?

- A novel statistical method called semantic map analysis is applied.
- Semantic connectivity maps show the association patterns of data obtained from the chronic hand eczema registries (CARPE) in Germany and Switzerland.

Summary

Background Hand eczema (HE) has a high incidence and prevalence, and is associated with disturbances of both physical and psychological well-being, and risk of persistence as chronic HE (CHE). Epidemiological studies on HE provided mainly descriptive and risk analyses, but pattern analyses of variables associated with HE, in particular CHE have not been explored so far.

Objectives To investigate and display the semantics of associations among variables of HE obtained by the Swiss and German registries of CHE (CARPE) to dissect patterns and novel links.

Methods This was a cross-sectional study on selected variables of the CARPE registries. Associations among variables were analyzed by means of an auto-associative system. A semantic connectivity map was generated by using the maximum spanning tree algorithm.

Results Baseline data sets of 1466 CHE patients (Switzerland: 199; Germany: 1267) were analyzed. Occupational exposure had the highest impact on CHE in the total and country cohorts. We identified two areas of exposure linked to corresponding occupations that clearly demarcated genders.

Conclusions This study using a semantic connectivity as novel method of data analysis reveals the complexity of features characterizing CHE as well as novel association patterns that deserve further investigations.

In the last years, hand eczema (HE) has gained increasing attention because of its high incidence and prevalence, disturbances of both physical and psychological well-being, negative socioeconomic consequences, and novel therapeutic options.[1, 2] Up to 68% of HE patients develop a chronic HE (CHE)[3], an observation highlighting the risk of HE of becoming a chronic health problem. In an European multicenter study, 52% of HE cases were related to occupational exposure.[4] Among occupational diseases, occupational skin diseases (OSD) account for 17% in Switzerland (www.suva.ch) and 31% in Germany (http://www.dguv.de). An increased risk for developing HE has been identified in individuals working in health care, cleaning, food industry, as hairdressers, construction and metal processing workers.[5-12] The spectrum of these high risk occupations points to external hazards, e.g. wet work, mechanical stress, and exposure to chemicals and allergens.[10] Both, irritant and allergic contact dermatitis have been considered as main and interacting mechanisms causing HE.[13,14] Moreover, childhood eczema and a history of atopy, especially in younger subjects, have been identified as risk factors for HE.[15] HE has been classified according to etiologic and morphologic criteria.[4, 13] However, etiology was not associated with clinical subtypes of HE.[16]

CHE was shown to impair the working ability in up to 37% of affected patients and entail job change or loss in 5 to 15%.[17, 18] Furthermore, the quality of life was significantly decreased in patients with HE correlating with disease severity.[17-19] Thus, unraveling causative factors and risks of HE, in particular CHE, seems indispensable to increase our understanding and to optimize the management of HE as well as to develop prevention strategies.

Recently, the Swiss and German CARPE (chronic hand eczema registry on long-term patient management) registries provided novel information on CHE.[17, 18] However, these previous analyses were mainly descriptive or focused on selected risk factors, and thus might not fully reflect the complexity of causes, triggers and consequences of CHE. To overcome this gap, we aimed at investigating the associations among variables (semantics). Here, we present a semantic connectivity map that was generated by using the maximum spanning tree algorithm. This map displays the best connections among variables based on their maximal reciprocal adjusted correlation.

Methods

CARPE had been initiated in 2009 in Germany and in 2011 in Switzerland as a prospective patient cohort study recruiting patients with CHE over a follow-up period of 2 years.[17, 18] The study has been approved by the local ethics committees. All patients gave written informed consent prior to enrollment. Here, data of the German and Swiss cohorts obtained at time of enrollment (baseline visit) were analyzed.

Patients

Patients with HE were eligible to participate in the CARPE study, if they met the following criteria: 1. Disease duration of at least 3 months or more than 2 flares within the last 12 months; 2. Recent treatment with topical corticosteroids for HE; 3. Failure to achieve long-term improvement despite adequate topical therapy; 4. Exclusion of other active severe skin diseases or acute skin infections interfering with the diagnosis of CHE.

Data

For the purpose of this study, an a priori selection of variables, independent of the data distribution, was considered in two different analyses (Supplementary Table 1). In the first analysis, we included demographics, patient history, clinical signs and symptoms, atopic diathesis, classification of HE based on morphology (vesicular, hyperkeratotic, fingertip dermatitis) and etiology (atopic HE, irritant and, allergic contact dermatitis), occupational status, occupation and work related variables, including exposure to allergens and irritants, severity and quality of life index. Atopic skin diathesis was based on a score ≥10 of the Erlangen Atopy Score.[20, 21]The severity of HE was assessed by the physicians global assessment (PGA) score (clear, almost clear, mild, moderate and severe) supported by a validated photographic guide.[22] Pruritus intensity was verbally obtained using a 4 point scale (no, mild, moderate and strong). The patients' health-related quality of life (HRQOL) was assessed based on the Dermatology Life Quality Index (DLQI) using the banding suggested by Hongbo et al.[23, 24] In the second analysis, we focused on HE treatment during the last 12 months (topical and systemic therapy), occupational status, present occupation as well as etiologic and morphologic features.

Statistical analysis

For descriptive purposes, data are presented as means with standard deviations (SD) or numbers with percentages for continuous and categorical variables, respectively. Continuous variables were categorized, for analysis purpose, using clinically meaningful thresholds as cut-offs.

Associations among selected variables in the CARPE registry were analyzed by means of an auto-associative system, as described previously[25-27], that is able to compute and display adjusted correlations between each pair of variables taking into account other covariates in the system. More specifically, after variable categorization, multiple logistic regression models are fitted by taking each time, sequentially, a variable as the predictor and the other as covariates. This process is reiterated until all variables in the model are processed. Finally, a symmetric square matrix of logistic regression coefficients (B) is produced along with their standard errors (SE). System weights are then computed by using inverse exponential transformation $sign(B) * (1 - \mathrm{e}^{-\mathrm{sign(B)}*\mathrm{B}})$ on regression coefficients, that maps associations in the interval [-1, 1].

A mathematical filter, the maximum spanning tree (MST) [28], is then applied to the matrix of weights and a semantic connectivity map is generated. This map represents the best connections among variables based on their maximal reciprocal adjusted correlation. To note, the MST selects positive associations ensuring to have normalized correlations between 0 and 1. 95% confidence intervals (CI) and p-values for normalized correlations were computed as well. In the semantic map, hubs of variables are detected, and related dependent variables converge to these hubs.

Adjustment by country was performed by combining, for every variable, regression coefficients in each stratum by means of fixed or random effect models. The choice of the model was automatically done based on I^2 heterogeneity index >56%.[29] The analysis was carried out using MATLAB v.7.8 (MathWorks, Natick, MA, US).

Results

Study population

Data of 1466 patients with CHE (Switzerland: 199; Germany 1267 patients) collected at 102 study centers were available. Detailed characteristics of both populations have been published elsewhere.[17, 18] In summary, the average age was 45.7 ± 13.8 years, 40.4 ± 14.2 and 46.5 ± 13.6 in the Swiss and German registry, respectively (Table 1). The overall proportion of females was 53.4% (50.7% in Switzerland and 53.8% in Germany). 13.9% of

CHE patients were non-employed (causes for non-employment were not specified). Among patients at work, most were employed in nursing and health care (17.4%), as metal workers, electricians and mechanics (14.6%) and in food and catering services (11.1%). The mean disease duration was 7.4 ± 8.9 years. 44.6% of patients had an atopic skin diathesis. Most patients had moderate (47.4%) or severe (21.5%) HE based on PGA assessment. The mean reported DLQI was 9.5 ± 6.1, with 39.8% of patients reporting a very or extremely large effect of the disease on their quality of life (DLQI >10).

Occupational exposure had the main impact on CHE

The semantic connectivity map showed the best linking among the selected variables of the pooled CARPE registry data from Germany and Switzerland (Fig. 1, Supporting information Tables S1, S2). Exposure to environmental factors, in particular occupational exposures, appeared in the center of the map indicating their high impact on CHE. Here, we found two areas: 1) exposure to wetness, detergents, disinfectants and wearing gloves; 2) exposure to solvents, chemicals, industrial oils, lubricants, refrigerants and mechanical stress. These exposure types were linked to corresponding occupations and gender. A quite clear demarcation between genders was seen with females associated with area 1 and males with area 2. Linked occupations were health care, hairdressing, cleaning, food processing/catering for females and construction, metal and chemical work for males.

CHE in females was connected to severe disease conditions and sick leave from work. Furthermore, CHE severity was strongly associated with moderate to severe pruritus, continuous disease course and high DLQI levels. Interestingly, CHE in females was connected to atopic predisposition and atopic HE. The analysis showed a link between the occupation as hairdresser with exposure to preservatives, as well as age under 30 and duration of the hand eczema between 2-5 years. Strikingly, CHE in food handling workers was strongly associated with ability to work/sick leave, but on the other hand with mild severity and pruritus. In contrast, males reported no or small effects of the disease on their life quality, and this was associated with minimal and moderate severity of the hand eczema and less than five episodes per year. In males, CHE was associated with previous allergies and allergic contact dermatitis. Notably, OSD were linked to male gender and industrial oil exposure, and showed a strong association with long duration of the hand eczema (≥ 6 years) and job loss or change. Workers exposed to chemicals had an associated CHE of the palms. Other eczema locations were not strongly associated with

gender, occupation or exposure. Considering the body mass index, there seemed to be a link between BMI >30, age over 50 years, fingertip dermatitis and hyperkeratotic eczema with additional involvement of the feet. Interestingly, when we varied and restricted the number of variables (Fig. 2, Supporting information Table S3), we observed an association of irritant contact dermatitis with cleaning, food processing, and health care work, while allergic contact dermatitis was connected with construction work, chemical industry and hairdressing.

Stratifying by country revealed a similar association of environmental, in particular occupational exposure in CHE patients with gender, disease severity, atopic predisposition, and effects on DLQI. When analyzing the Swiss registry data (Supporting information Fig. S1, Table S4), we noted a strong association between obesity (BMI >30) and severe CHE as well as with fingertip dermatitis, eczema localization on the forearms and intensive pruritus. Here, OSD was highly associated with working with chemicals, allergic contact dermatitis and again job loss or change. The analysis of the German registry (Supporting information Fig. S2, Table S5) revealed that severe HE and associated intense pruritus were linked to the diagnosis of hyperkeratotic eczema, as well as to OSD and job loss or change. In addition, it clearly showed that CHE in hairdressers was connected with multiple conditions including wearing gloves, wet work and preservative exposure as well as interdigital eczema localization.

Corticosteroids as main therapy

Next, we were interested in the associations among treatments over the last 12 months, present occupation and subtypes of CHE (Fig. 2, Supporting information Table S3). In the center of the map, we found both systemic and topical corticosteroids. Systemic corticosteroids were mainly used for the treatment of vesicular eczema and in CHE patients working in metal industry. Moreover, the administration of systemic corticosteroids was connected with the use of potent and very potent topical corticosteroids. Work as cleaner and presence of irritant contact dermatitis were associated with the use of mild/moderate and potent topical corticosteroids. Hyperkeratotic eczema was preferably treated with very potent topical corticosteroids, salicylic acid and urea. Among CHE subtypes, hyperkeratotic eczema was connected to second line therapies such as alitretinoin, UV therapy including PUVA, and topical calcineurin inhibitors. When we stratified the data by countries, we observed slightly different association patterns in the

German and Swiss registries. In the Swiss registry (Supporting information Fig. S3, Table S6) the distribution was similar to the overall map. Systemic corticosteroids appeared in the center of the graph and were associated with topical corticosteroid therapy, but also with vesicular eczema, work in health care and chemical industry. Interestingly, the German registry data (Supporting information Fig. S4, Table S7) indicated salicylic acid as main topical therapy for hyperkeratotic eczema together with other treatment options including potent and very potent corticosteroids, alitretinoin and PUVA therapy.

Discussion

Here, we provide a semantic connectivity map that presents the best connections among variables of CHE obtained from registries in Germany and Switzerland. It should be noted that the data refer to more severe cases of HE as patients with a chronic and/or recurrent disease, recent therapy with topical corticosteroids and a failure to achieve long-term improvement despite adequate topical therapies were enrolled. Previous studies mainly evaluated the impact of specific variables on CHE and often in selected groups of individuals. In comparison with conventional statistical analyses, our study had the advantage of displaying multiple data and associations among each other in one map, thus providing a comprehensive view on CHE. Different exposure areas and interesting novel associations between variables emerged from this analysis. To note, these associations were found in an exploratory cross-sectional analysis and do not necessarily indicate a causal relationship.

A striking result of the semantic map analysis was the clear demarcation between genders and subordinated associations with occupations, exposure, HE etiology, severity and quality of life. Population-based studies reported a higher prevalence of HE in females than males.[1, 30-34] This female predominance already became evident in cohorts of adolescents and young adults in which the prevalence of HE was twice as high in females compared to males.[35-37] Gender was not related to the prognosis of HE in a follow-up study (38). However, applying innovative statistical methods, our study indicates that gender may be an important factor to discriminate between different patterns of disease characteristics.

Previously, gender differences of HE prevalence have been attributed to exposure, both occupational and non-occupational ones.[39, 40] In our semantic map, environmental, in

particular occupational exposures were placed in the center suggesting a high impact on CHE. Already a previous study stated HE was more common among people reporting occupational exposure to chemicals, water, detergents as well as dust and dry dirt.[39] Our study showed that wet work and exposure to detergents and disinfectants as well as wearing gloves were associated with working in healthcare, cleaning, food processing or as hairdresser/beautician and thus with female sex. A recent study demonstrating that occupational water exposure was almost twice as high in women than in men, and significantly higher in high-risk occupations in service and healthcare, in particular kitchen work, restaurant work, cleaning and hairdressing, as compared with non-high-risk occupations.[41] Among people working in health care, those with hand dermatitis were more likely to wash hands frequently and wear gloves for more hours per day.[42]

Based on the etiopathology, most HE cases have been classified as irritant or allergic contact dermatitis or as a combination of both.[4, 13, 16] Atopic diseases and childhood eczema have been identified as risk factor for the prevalence, persistence and severity of HE.[6, 30, 36, 43-46] In the semantic map, an atopic predisposition and the diagnosis of atopic hand eczema were associated with female gender and connected to disease severity confirming previous observations.[47] Interestingly, this association was not observed in our previous multivariable analysis.[18] Notably, the exposure to industrial oils, lubricants, solvents and corresponding, mainly male-dominated occupations were linked to allergic contact dermatitis in our study cohorts. These observations were in agreement with others reporting a lower rate of atopy but high rates of contact allergy in low-qualified occupations.[10, 48] Allergic contact sensitization has been identified as risk factor for more severe and prolonged HE[30, 44], while others did not find any correlation.[45] Recently, a strong, positive association between loss-of-function mutations of filaggrin, an epidermal barrier protein, and the presence of contact dermatitis was found in construction workers[49] supporting our observation that construction work was linked to irritant contact dermatitis on our map.

In line with previous publications on the lack of clear associations between morphology and etiopathologic subtypes of HE[4, 13,16], we found areas of clinical subtypes and localization that both were not linked to etiologic parameters. When the number of parameters for the semantic map analysis was reduced, the disconnectedness of etiologic subtypes and morphologic characteristics became even more obvious. According to our

semantic map, hyperkeratotic eczema was more common among males and linked to age and BMI, supporting recent observations.[47]

Both Swiss and German registry analyses indicated high rates of workers on sick leave (>35%) during the past 12 months, in particular in high-risk occupations.[17, 18] According to the semantic map, sick leave was associated with HE severity, female gender and working with foods confirming recent observations.[38, 46, 50] In addition to sick leave, job change or loss have been considered major consequences of HE in particular occupational HE.[38, 45, 50] Our map clearly showed a link of job loss or change with persistent HE as well as OSD, occupational exposure and male gender, and thus provided additional information to the conventional data analysis.[17, 18]

HE has been shown to have immense negative effects on patients quality of life.[17-19, 38] In the Swiss cohort, female gender, pruritus and wearing gloves were the main factors contributing to a diminished quality of life.[18] Recent studies reported similar or higher DLQI levels in woman despite the fact that they were less severe affected than man.[19, 34, 51] In contrast, our map demonstrated complex associations of severe CHE with moderate to severe pruritus and continuous disease course that are related to elevated DLQI levels that are further linked to sick leave and female gender.

For the management of HE, a stepwise approach has been proposed in national and international guidelines.[2, 52-54] The analyses of the CARPE registry data showed a broad spectrum of therapeutic measures was applied, but did not rank them.[17, 18] Topical corticosteroids have been recommended as first line therapy, and systemic corticosteroids should only be used as short-term intervention in case of acute severe exacerbations. Therefore, the link between systemic corticosteroids with the vesicular HE subtypes may indicate that these CHE patients required a very potent therapy. Second line therapies such as PUVA-UV therapy and alitretinoin were mainly used for hyperkeratotic eczema and fingertip dermatitis. Indeed, alitretinoin was shown to have the highest response rate in patients with hyperkeratotic HE and fingertip dermatitis.[55] The links between therapeutic measures and HE subtypes let suggest that the type of treatment was selected based on morphology rather than etiology or exposure.

The strength of our study is, that, by applying the semantic connectivity analysis, we are able to synthesize and display association patterns of a huge number of variables obtained from the CARPE registries in Germany and Switzerland. Some of the feature associations could confirm previous observations. The limitation of the study is that the method applied is entirely exploratory. This study did not focus on showing correlations between variables by applying conventional statistical methods. Therefore, patterns emerging from the semantic maps that have not been demonstrated so far, should give reasons to further research, e.g. to study the impact of atopy on etiological subtypes of HE, or to develop differential therapeutic regimens for subtypes of HE.

Acknowledgement

The Carpe registry was supported by research grants from Basilea Pharmaceutica International AG and Glaxo SmithKline AG Switzerland. DS, VM, AB, and SM participated in the COST action TD1206 StanDerm.

References

1. Thyssen JP, Johansen JD, Linneberg A, Menné T. The epidemiology of hand eczema in the general population--prevalence and main findings. *Contact Dermatitis* 2010: **62**: 75-87.
2. Diepgen TL, Andersen KE, Chosidow O, et al. Guidelines for diagnosis, prevention and treatment of hand eczema. *J Dtsch Dermatol Ges* 2015: **13**: e1-22.
3. Lerbaek A, Kyvik KO, Ravn H, et al. Clinical characteristics and consequences of hand eczema - an 8-year follow-up study of a population-based twin cohort. *Contact Dermatitis* 2008: **58**: 210-216.
4. Diepgen TL, Andersen KE, Brandao FM, et al. Hand eczema classification: a crosssectional, multicentre study of the aetiology and morphology of hand eczema. *Br J Dermatol* 2009: **160**: 353–358.
5. van der Meer EW, Boot CR, van der Gulden JW, et al. Hand eczema among healthcare professionals in the Netherlands: prevalence, absenteeism, and presenteeism. *Contact Dermatitis* 2013: **69**: 164-171.

6. Ibler KS, Jemec GB, Flyvholm MA, et al. Hand eczema: prevalence and risk factors of hand eczema in a population of 2274 healthcare workers. *Contact Dermatitis* 2012: **67** :200-207.
7. Weisshaar E, Radulescu M, Soder S, et al. Secondary individual prevention of occupational skin diseases in health care workers, cleaners and kitchen employees: aims, experiences and descriptive results. *Int Arch Occup Environ Health* 2007: **80** :477-484.
8. Carøe TK, Ebbehøj NE, Agner T. Occupational dermatitis in hairdressers - influence of individual and environmental factors. *Contact Dermatitis* 2016 Oct 6. doi: 10.1111/cod.12686.
9. Lysdal SH, Søsted H, Andersen KE, Johansen JD. Hand eczema in hairdressers: a Danish register-based study of the prevalence of hand eczema and its career consequences. *Contact Dermatitis* 2011: **65**: 151-158.
10. Schwensen JF, Menné T, Veien NK, et al. Occupational contact dermatitis in blue-collar workers: results from a multicentre study from the Danish Contact Dermatitis Group (2003-2012). *Contact Dermatitis*. 2014: **71**: 348-355.
11. Apfelbacher CJ, Radulescu M, Diepgen TL, Funke U. Occurrence and prognosis of hand eczema in the car industry: results from the PACO follow-up study (PACO II). *Contact Dermatitis* 2008: **58**: 322-329.
12. Gruvberger B, Isaksson M, Frick M, et al. Occupational dermatoses in a metalworking plant. *Contact Dermatitis*. 2003: **48**: 80-86.
13. Agner T, Aalto-Korte K, Andersen KE, et al. Classification of hand eczema. *J Eur Acad Dermatol Venereol* 2015: **29**: 2417-2422.
14. Molin S, Diepgen TL, Ruzicka T, Prinz JC. Diagnosing chronic hand eczema by an algorithm: a tool for classification in clinical practice. *Clin Exp Dermatol* 2011: **36**: 595-601.
15. Meding B, Järvholm B. Incidence of hand eczema-a population-based retrospective study. *J Invest Dermatol* 2004: **122**: 873-877.
16. Johansen JD, Hald M, Andersen BL, Laurberg G, et al. Classification of hand eczema: clinical and aetiological types. Based on the guideline of the Danish Contact Dermatitis Group. *Contact Dermatitis* 2011: **65**: 13-21.
17. Apfelbacher C, Molin S, Weisshaar E, et al. Characteristics and provision of care in patients with chronic hand eczema: updated data from the CARPE registry. *Acta Derm Venereol* 2014: **94**: 163-167.

18. Cazzaniga S, Ballmer-Weber BK, Gräni N, et al. Medical, psychological and socio-economic implications of chronic hand eczema: a cross-sectional study. *J Eur Acad Dermatol Venereol* 2016: **30**: 628-637.
19. Agner T, Andersen KE, Brandao FM, et al. Hand eczema severity and quality of life: a cross-sectional, multicentre study of hand eczema patients. *Contact Dermatitis*. 2008: **59**: 43-47.
20. Diepgen TL, Fartasch M, Hornstein OP. Criteria of atopic skin diathesis. *Derm Beruf Umwelt* 1991: **39**: 79-83.
21. Diepgen TL, Sauerbrei W, Fartasch M. Development and validation of diagnostic scores for atopic dermatitis incorporating criteria of data quality and practical usefulness. *J Clin Epidemiol* 1996: **49**: 1031-1038.
22. Coenraads PJ, Van Der Walle H, Thestrup-Pedersen K, et al. Construction and validation of a photographic guide for assessing severity of chronic hand dermatitis. *Br J Dermatol* 2005: **152**: 296-301.
23. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI) – a simple practical measure for routine clinical use. *Clin Exp Dermatol* 1994: **19**: 210-216.
24. Hongbo Y, Thomas CL, Harrison MA, et al. Translating the science of quality of life into practice: What do dermatology life quality index scores mean? *J Invest Dermatol* 2005: **125**: 659–664.
25. Usui M, Nanbu Y, Oka K, et al. Genetic relatedness between Japanese and European isolates of Clostridium difficile originating from piglets and their risk associated with human health. *Front Microbiol* 2014: **5**: 513.
26. Roetzer A, Diel R, Kohl TA, et al. Whole Genome Sequencing versus Traditional Genotyping for Investigation of a Mycobacterium tuberculosis Outbreak: A Longitudinal Molecular Epidemiological Study. *PLoS Med* 2013: **10**: e1001387.
27. Grossi E, Cazzaniga S, Crotti S, et al. The constellation of dietary factors in adolescent acne: a semantic connectivity map approach. *J Eur Acad Dermatol Venereol* 2016: **30**: 96-100.
28. Pemmaraju S, Skiena S. Combinatorics and Graph Theory in Mathematica. In: Computational Discrete Mathematics, Pemmaraju S, Skiena S (eds.): Cambridge, Cambridge University Press, 2003: 336-337.
29. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statist Med* 2002: **21**: 1539-1558.

30. Meding B. Epidemiology of hand eczema in an industrial city. *Acta Derm Venereol Suppl (Stockh)* 1990: **153**: 1-43.
31. Montnémery P, Nihlén U, Löfdahl CG, et al. Prevalence of hand eczema in an adult Swedish population and the relationship to risk occupation and smoking. *Acta Derm Venereol* 2005: **85**: 429-432.
32. Mortz CG, Lauritsen JM, Bindslev-Jensen C, Andersen KE. Prevalence of atopic dermatitis, asthma, allergic rhinitis, and hand and contact dermatitis in adolescents. The Odense Adolescence Cohort Study on Atopic Diseases and Dermatitis. *Br J Dermatol* 200: **144**: 523-532.
33. Dalgard F, Svensson A, Sundby J, Dalgard OS. Self-reported skin morbidity and mental health. A population survey among adults in a Norwegian city. *Br J Dermatol* 2005: **153**: 145-149.
34. Bingefors K, Lindberg M, Isacson D. Quality of life, use of topical medications and socio-economic data in hand eczema: a Swedish nationwide survey. *Acta Derm Venereol* 2011: **91**: 452-458.
35. Johannisson A, Pontén A, Svensson Å. Prevalence, incidence and predictive factors for hand eczema in young adults - a follow-up study. *BMC Dermatol* 2013: **29**: 13-14.
36. Mortz CG, Bindslev-Jensen C, Andersen KE. Hand eczema in The Odense Adolescence Cohort Study on Atopic Diseases and Dermatitis (TOACS): prevalence, incidence and risk factors from adolescence to adulthood. *Br J Dermatol* 2014: **171**: 313-323.
37. Grönhagen CM, Lidén C, Bergström A, et al. Prevalence and incidence of hand eczema in adolescence: report from BAMSE--a population-based birth cohort. *Br J Dermatol* 2014: **171**: 609-614.
38. Petersen AH, Johansen JD, Hald M. Hand eczema—prognosis and consequences: a 7-year follow-up study. *Br J Dermatol* 2014: **171**: 1428-1433.
39. Meding B. Differences between the sexes with regard to work-related skin disease. *Contact Dermatitis* 2000: **43**: 65-71.
40. Schwensen JF, Friis UF, Menné T, Johansen JD. One thousand cases of severe occupational contact dermatitis. *Contact Dermatitis* 2013: **68**: 259-268.
41. Meding B, Grönhagen CM, Bergström A, et al. Water Exposure on the Hands in Adolescents: A Report from the BAMSE Cohort. *Acta Derm Venereol* 2016 Jul 7. doi: 10.2340/00015555-2505.

42. Nichol K, Copes R, Spielmann S, et al. Workplace screening for hand dermatitis: a pilot study. *Occup Med (Lond)* 2016: **66**: 46-49.
43. Grönhagen C, Lidén C, Wahlgren CF, et al. Hand eczema and atopic dermatitis in adolescents: a prospective cohort study from the BAMSE project. *Br J Dermatol* 2015: **173**: 1175-1182.
44. Heede NG, Thyssen JP, Thuesen BH, et al. Predictive factors of self-reported hand eczema in adult Danes: a population-based cohort study with 5-year follow-up. *Br J Dermatol* 2016: **175**: 287-295.
45. Mälkönen T, Alanko K, Jolanki R, et al. Long-term follow-up study of occupational hand eczema. *Br J Dermatol* 2010: **163**: 999-1006.
46. Cvetkovski RS, Rothman KJ, Olsen J, et al. Relation between diagnoses on severity, sick leave and loss of job among patients with occupational hand eczema. *Br J Dermatol* 2005: **152**: 93-98.
47. Brans R, John SM. Clinical patterns and associated factors in patients with hand eczema of primarily occupational origin. *J Eur Acad Dermatol Venereol* 2016: **30**: 798-805.
48. Skoet R, Olsen J, Mathiesen B, et al. A survey of occupational hand eczema in Denmark. *Contact Dermatitis* 2004: **51**: 159-166.
49. Timmerman JG, Heederik D, Spee T, et al. Contact dermatitis in the construction industry: the role of filaggrin loss-of-function mutations. *Br J Dermatol* 2016: **174**: 348-355.
50. Vester L, Thyssen JP, Menné T, Johansen JD. Consequences of occupational food-related hand dermatoses with a focus on protein contact dermatitis. *Contact Dermatitis* 2012: **67**: 328-333.
51. Mollerup A, Veien NK, Johansen JD. An analysis of gender differences in patients with hand eczema - everyday exposures, severity, and consequences. *Contact Dermatitis* 2014: **71**: 21-30.
52. Diepgen TL, Elsner P, Schliemann S, et al. Guideline on the management of hand eczema ICD-10 Code: L20. L23. L24. L25. L30. *J Dtsch Dermatol Ges* 2009: **7** (Suppl. 3): S1-16.
53. Menné T, Johansen JD, Sommerlund M, Veien NK. Hand eczema guidelines based on the Danish guidelines for the diagnosis and treatment of hand eczema. *Contact Dermatitis* 2011: **65**: 3-12.

54. English J, Aldridge R, Gawkrodger DJ, et al. Consensus statement on the management of chronic hand eczema. *Clin Exp Dermatol* 2009: **34**: 761-769.
55. Ruzicka T, Lynde CW, Jemec GB, et al. Efficacy and safety of oral alitretinoin (9-cis retinoic acid) in patients with severe chronic hand eczema refractory to topical corticosteroids: results of a randomized, double-blind, placebo-controlled, multicentre trial. *Br J Dermatol* 2008: **158**: 808-817.

Tables

Table 1 - Demographics and clinical features of the population included in the CARPE registry, overall and in strata of each country

		Overall (N=1466)	**Swiss (N=199)**	**German (N=1267)**
		N* (%)	**N* (%)**	**N* (%)**
Age	*(mean, SD)*	*45.7 (13.8)*	*40.4 (14.2)*	*46.5 (13.6)*
	<30	257 (17.5%)	56 (28.1%)	201 (15.9%)
	30 - 49	559 (38.1%)	83 (41.7%)	476 (37.6%)
	50+	650 (44.3%)	60 (30.1%)	590 (46.6%)
Gender	Male	683 (46.6%)	98 (49.3%)	585 (46.2%)
	Female	783 (53.4%)	101 (50.7%)	682 (53.8%)
BMI, kg/m^2	*(mean, SD)*	*26.6 (5.0)*	*25.9 (4.7)*	*26.7 (5.0)*
	<25	582 (39.9%)	91 (46.2%)	491 (38.9%)
	25 - 29.9	584 (40.1%)	74 (37.6%)	510 (40.4%)
	30+	292 (20.0%)	32 (16.2%)	260 (20.6%)
Present occupation	Construction/ mineral extraction	75 (5.1%)	16 (8.0%)	59 (4.7%)
	Printing/ processing of chemicals, textiles and plastics	60 (4.1%)	11 (5.5%)	49 (3.9%)
	Hairdressers and	58 (4.0%)	5 (2.5%)	53 (4.2%)

		Overall (N=1466)	Swiss (N=199)	German (N=1267)
		N* (%)	N* (%)	N* (%)
	beauticians			
	Food and catering	163 (11.1%)	26 (13.1%)	137 (10.8%)
	Metal workers and electricians/ mechanics	214 (14.6%)	19 (9.5%)	195 (15.4%)
	Nursing and health care	255 (17.4%)	24 (12.1%)	231 (18.2%)
	Cleaning	74 (5.1%)	15 (7.5%)	59 (4.7%)
	Office and administration	130 (8.9%)	29 (14.6%)	101 (8.0%)
	Other	233 (15.9%)	21 (10.6%)	212 (16.7%)
	Not working	204 (13.9%)	33 (16.6%)	171 (13.5%)
Disease duration, yrs	*(mean, SD)*	*7.4 (8.9)*	*6.6 (8.3)*	*7.5 (9.0)*
	<2	385 (26.4%)	73 (37.1%)	312 (24.7%)
	2 - 5	486 (33.3%)	50 (25.4%)	436 (34.5%)
	6+	589 (40.3%)	74 (37.6%)	515 (40.8%)
Atopic diathesis	No	806 (55.4%)	89 (45.9%)	717 (56.9%)
	Yes	649 (44.6%)	105 (54.1%)	544 (43.1%)
PGA	Clear/ almost clear	142 (9.7%)	11 (5.5%)	131 (10.4%)
	Mild	312	47 (23.6%)	265

		Overall (N=1466)	Swiss (N=199)	German (N=1267)
		N* (%)	N* (%)	N* (%)
		(21.3%)		(21.0%)
	Moderate	694 (47.4%)	112 (56.3%)	582 (46.0%)
	Severe	315 (21.5%)	29 (14.6%)	286 (22.6%)
DLQI	*(mean, SD)*	*9.5 (6.1)*	*9.7 (5.7)*	*9.5 (6.1)*
	No/ small	414 (29.4%)	50 (26.0%)	364 (29.9%)
	Moderate	434 (30.8%)	66 (34.4%)	368 (30.3%)
	Very large/ extremely large	560 (39.8%)	76 (39.6%)	484 (39.8%)

BMI: body mass index, PGA: physician global assessment, DLQI: dermatology life quality index

* numbers may not add up to the total due to missing or unknown data.

Figure legends

Figure 1 Semantic map analysis of the pooled CARPE registry data. The best linking among selected variables is shown. Exposure to environmental factors and occupations are marked by a continuous line. Exposure types (area 1: exposure to wetness, detergents, disinfectants and wearing gloves, and area 2: exposure to solvents, chemicals, industrial oils, lubricants, refrigerants and mechanical stress) are marked by a dashed line. The numbers indicate normalized correlations (between 0 and 1). The line thickness corresponds to the strength of association (thin line, <0.6; medium line, 0.6 - 0.8; thick line, >0.8).

Figure 2 Sematic map of associations among treatment, present occupation and CHE subtypes of the pooled CARPE registry data. The numbers indicate normalized correlations (between 0 and 1). The line thickness corresponds to the strength of association (thin line, <0.6; medium line, 0.6 - 0.8; thick line, >0.8).

Supporting information

Supplementary Figure S1 Semantic map analysis of the Swiss CARPE registry data. The figure shows the best linking among selected variables. The numbers indicate normalized correlations (between 0 and 1). The line thickness corresponds to the strength of association (thin line, <0.6; medium line, 0.6 - 0.8; thick line, >0.8).

Supplementary Figure S2 Semantic map analysis of the German CARPE registry data. The figure shows the best linking among selected variables. The numbers indicate normalized correlations (between 0 and 1). The line thickness corresponds to the strength of association (thin line, <0.6; medium line, 0.6 - 0.8; thick line, >0.8).

Supplementary Figure S3 Semantic map of associations among treatment, present occupation and CHE subtypes in the Swiss CARPE cohort. The numbers indicate normalized correlations (between 0 and 1). The line thickness corresponds to the strength of association (thin line, <0.6; medium line, 0.6 - 0.8; thick line, >0.8).

Supplementary Figure S4 Semantic map of associations among treatment, present occupation and CHE subtypes in the German CARPE cohort. The numbers indicate normalized correlations (between 0 and 1). The line thickness corresponds to the strength of association (thin line, <0.6; medium line, 0.6 - 0.8; thick line, >0.8).

Supplementary Table S1 - List of selected variables of the CARPE registry with their categorizations and abbreviations used in the semantic map analysis.

Variable	Category	Abbreviation
Gender	Male	Male
	Female	Female
Age (years)	<30	Age_<30
	30 - 49	Age_30-49
	50+	Age_50+
BMI (kg/m^2)	<25	BMI_<25
	25 - 29.9	BMI_25-29
	30+	BMI_30+
History of previous allergy	No	Prev_allergy_no
	Yes	Prev_allergy_yes
Atopic diathesis	No	Atopic_diathesis_no
	Yes	Atopic_diathesis_yes
Disease duration (years)	<2	Duration_<2
	2 - 5	Duration_2-5
	6+	Duration_6+
Number of HE episodes (in the last 12 months)	<5	Episodes_<5
	≥5	Episodes_5+
	Continuous	Episodes_cont
HE localization	Back hand	Back_hand
	Palm	Palm
	Wrist	Wrist
	Interdigital	Interdigital
	Forearms	Forearms
	Feet	Feet
HE diagnosis	Allergic contact dermatitis	Allergic_contact_dermat
	Irritant contact dermatitis	Irritant_contact_dermat
	Atopic hand eczema	Atopic_hand_eczema
	Hyperkeratotic eczema	Hyperkeratotic_eczema
	Fingertip dermatitis	Fingertip_dermat
	Vesicular eczema	Vesicular_eczema
PGA	Clear/ almost clear	PGA_almost_clear

Variable	Category	Abbreviation
	Mild	PGA_mild
	Moderate	PGA_moderate
	Severe	PGA_severe
DLQI	No/small	DLQI_no-small
	Moderate	DLQI_moderate
	Very large/ extremely large	DLQI_large
Present occupation*	Construction/ mineral extraction	Work_construction
	Printing/ processing of chemicals, textiles and plastics	Work_chemicals
	Hairdressers and beauticians	Work_hairdressing
	Food and catering	Work_food
	Metal workers and electricians/ mechanics	Work_metal
	Nursing and health care	Work_health
	Cleaning	Work_cleaning
OSD	Yes	OSD
Job loss or change (due to OSD)	Yes	Job_loss-change
Sick leave from work (due to OSD)	Yes	Sick_leave
Patient's is able to work	Yes	Able_to_work
Exposure	Wet work	Wet_exp
	Detergents	Detergents_exp
	Disinfectants	Disinfectants_exp
	Lubrificants/ refrigerants	Lubri-refrigerants_exp
	Solvents	Solvents_exp
	Industrial oils	Industrial_oils_exp
	Mechanical stress	Mechanical_stress_exp
	Preservatives	Preservatives_exp
	Gloves	Gloves_exp
Treatment for HE (in the last 12 months)	Mild/ moderate corticosteroids	Cortic_mild-mod
	Potent corticosteroids	Cortic_potent
	Very potent corticosteroids	Cortic_very_potent
	Salicylic acid	Salicylic_acid
	Topical calcineurin inhibitors	Calcineurin_inhibitors
	Urea	Urea
	Alitretinoin	Alitretinoin

Variable	Category	Abbreviation
	Systemic corticosteroids	Cortic_systemic
	PUVA/ UV therapies	PUVA-UV_therapies

HE: hand eczema, BMI: body mass index, PGA: physician global assessment, DLQI: Dermatology Life Quality Index, OSD: occupational skin diseases

* At risk occupations

Supplementary Table S2 - Normalized correlation between variables as shown in Figure 1

Variables pair	Correlation (95% CI)*	P-value
Female & Work_cleaning	0.731 (0.358, 0.887)	0.003
Female & Atopic_diathesis_yes	0.628 (-0.338, 0.908)	0.167
Female & Detergents_exp	0.837 (-0.193, 0.979)	0.08
Male & Work_construction	0.957 (0.808, 0.991)	<0.001
Male & Atopic_diathesis_no	0.628 (-0.338, 0.908)	0.167
Male & DLQI_no-small	0.862 (-0.867, 0.997)	0.332
Age_<30 & Duration_2-5	0.428 (0.202, 0.590)	0.001
Age_<30 & BMI_<25	0.732 (0.625, 0.808)	<0.001
BMI_<25 & DLQI_moderate	0.500 (-0.650, 0.912)	0.435
BMI_30+ & Age_50+	0.507 (0.322, 0.641)	<0.001
BMI_30+ & Fingertip_dermat	0.652 (-0.694, 0.963)	0.356
OSD & Job_loss-change	0.894 (0.803, 0.943)	<0.001
Work_construction & BMI_30+	0.678 (-0.499, 0.948)	0.223
Work_chemicals & Palm	0.626 (-0.045, 0.866)	0.061
Work_hairdressing & Age_<30	0.679 (0.370, 0.836)	<0.001
Work_hairdressing & BMI_25-29	0.599 (-0.941, 0.990)	0.632
Work_hairdressing & Preservatives_exp	0.676 (0.305, 0.849)	0.004
Work_food & Prev _allergy_no	0.545 (-0.452, 0.886)	0.266
Work_food & PGA_mild	0.700 (-0.803, 0.982)	0.404
Work_metal & Mechanical_stress_exp	0.762 (0.600, 0.858)	<0.001
Work_health & Gloves_exp	0.801 (0.615, 0.897)	<0.001
Work_cleaning & Sick_leave	0.617 (-0.257, 0.891)	0.135
Able_to_work & Work_food	0.842 (-0.843, 0.996)	0.329
Sick_leave & Duration_<2	0.611 (0.464, 0.718)	<0.001
Sick_leave & Able_to_work	0.845 (0.470, 0.955)	0.003

Variables pair	Correlation (95% CI)*	P-value
Sick_leave & DLQI_large	0.609 (-0.257, 0.886)	0.137
Job_loss-change & Duration_6+	0.656 (0.404, 0.802)	<0.001
Prev _allergy_yes & Allergic_contact_dermat	0.968 (0.834, 0.994)	<0.001
Wrist & Back_hand	0.737 (-0.111, 0.939)	0.072
Wrist & Interdigital	0.522 (0.289, 0.679)	<0.001
Wrist & Forearms	0.931 (0.891, 0.957)	<0.001
Wrist & PGA_moderate	0.505 (-0.692, 0.924)	0.464
Vesicular_eczema & Episodes_5+	0.495 (0.263, 0.653)	<0.001
Hyperkeratotic_eczema & Feet	0.459 (0.234, 0.618)	<0.001
Fingertip_dermat & Irritant_contact_dermat	0.538 (0.222, 0.725)	0.004
Fingertip_dermat & Vesicular_eczema	0.575 (0.250, 0.759)	0.003
Fingertip_dermat & Hyperkeratotic_eczema	0.585 (0.126, 0.803)	0.021
PGA_severe & Episodes_cont	0.553 (-0.555, 0.911)	0.328
PGA_severe & Pruritus_moderate	0.362 (-0.446, 0.775)	0.397
PGA_severe & Pruritus_strong	0.704 (0.587, 0.787)	<0.001
PGA_mild & Pruritus_mild	0.573 (-0.347, 0.881)	0.192
PGA_almost_clear & Episodes_<5	0.467 (0.133, 0.672)	0.011
PGA_almost_clear & Wrist	0.748 (-0.798, 0.987)	0.364
PGA_almost_clear & Pruritus_no	0.850 (0.365, 0.965)	0.01
Atopic_diathesis_yes & Atopic_hand_eczema	0.898 (0.733, 0.961)	<0.001
Wet_exp & Age_30-49	0.562 (-0.573, 0.918)	0.334
Detergents_exp & Wet_exp	0.875 (0.826, 0.910)	<0.001
Detergents_exp & Disinfectants_exp	0.835 (0.717, 0.903)	<0.001
Detergents_exp & Solvents_exp	0.660 (0.450, 0.790)	<0.001
Disinfectants_exp & Work_health	0.979 (0.810, 0.998)	<0.001
Lubri-refrigerants_exp & Work_metal	0.922 (0.866, 0.954)	<0.001
Lubri-refrigerants_exp & Prev _allergy_yes	0.589 (0.291, 0.762)	0.001
Solvents_exp & Work_chemicals	0.786 (0.579, 0.891)	<0.001
Solvents_exp & Industrial_oils_exp	0.888 (0.812, 0.933)	<0.001
Industrial_oils_exp & Male	0.828 (0.701, 0.900)	<0.001
Industrial_oils_exp & OSD	0.700 (0.494, 0.822)	<0.001

Variables pair	Correlation (95% CI)*	P-value
Industrial_oils_exp & Lubri-refrigerants_exp	0.940 (0.882, 0.970)	<0.001
Gloves_exp & Work_hairdressing	0.775 (0.162, 0.940)	0.026
DLQI_no-small & PGA_almost_clear	0.739 (0.610, 0.825)	<0.001
DLQI_large & PGA_severe	0.597 (0.447, 0.706)	<0.001

CI: confidence interval

* Correlation and its 95% CI are normalized in the interval [-1, 1]

Supplementary Table S3 - Normalized correlation between variables as shown in Figure 2

Variables pair	Correlation (95% CI)*	P-value
Work_construction & Allergic_contact_dermat	0.416 (-0.001, 0.659)	0.05
Work_health & Atopic_hand_eczema	0.460 (0.263, 0.604)	<0.001
Work_cleaning & Cortic_mild-mod	0.556 (0.201, 0.754)	0.007
Work_cleaning & Cortic_potent	0.554 (0.176, 0.758)	0.01
Irritant_contact_dermat & Work_food	0.390 (0.113, 0.581)	0.01
Irritant_contact_dermat & Work_health	0.524 (0.350, 0.651)	<0.001
Irritant_contact_dermat & Work_cleaning	0.511 (0.152, 0.718)	0.011
Allergic_contact_dermat & Work_chemicals	0.485 (-0.449, 0.854)	0.302
Allergic_contact_dermat & Work_hairdressing	0.556 (0.239, 0.741)	0.003
Allergic_contact_dermat & Irritant_contact_dermat	0.455 (-0.060, 0.721)	0.075
Hyperkeratotic_eczema & Fingertip_dermat	0.622 (0.241, 0.812)	0.006
Hyperkeratotic_eczema & Salicylic_acid	0.616 (0.387, 0.760)	<0.001
Cortic_potent & Cortic_systemic	0.503 (-0.643, 0.912)	0.428
Cortic_very_potent & Hyperkeratotic_eczema	0.561 (-0.231, 0.852)	0.137
Salicylic_acid & Urea	0.407 (0.186, 0.568)	0.001
Salicylic_acid & PUVA-UV_therapies	0.713 (0.225, 0.894)	0.014
Salicylic_acid & Alitretinoin	0.499 (0.298, 0.642)	<0.001
Cortic_systemic & Work_metal	0.427 (-0.594, 0.867)	0.454
Cortic_systemic & Vesicular_eczema	0.577 (-0.152, 0.849)	0.1
Cortic_systemic & Cortic_very_potent	0.790 (-0.299, 0.969)	0.11
Alitretinoin & Calcineurin_inhibitors	0.536 (-0.152, 0.817)	0.107

CI: confidence interval

* Correlation and its 95% CI are normalized in the interval [-1, 1]

Supplementary Table S4 - Normalized correlation between variables as shown in Supplementary Figure S1

Variables pair	Correlation (95% CI)*	P-value
Female & Atopic_diathesis_yes	0.844 (0.423, 0.958)	0.005
Female & Detergents_exp	0.951 (0.749, 0.991)	<0.001
Male & Work_construction	0.990 (-1.000, 1.000)	1
Male & Atopic_diathesis_no	0.844 (0.423, 0.958)	0.005
Male & DLQI_no-small	0.985 (0.821, 0.999)	<0.001
BMI_<25 & DLQI_moderate	0.813 (0.411, 0.941)	0.004
BMI_30+ & Forearms	0.919 (0.031, 0.993)	0.047
BMI_30+ & Fingertip_dermat	0.919 (0.179, 0.992)	0.033
BMI_30+ & PGA_severe	0.872 (0.295, 0.977)	0.018
Episodes_<5 & PGA_moderate	0.972 (-0.945, 1.000)	0.279
Episodes_cont & Work_hairdressing	0.990 (-1.000, 1.000)	1
OSD & Job_loss-change	0.967 (0.772, 0.995)	<0.001
OSD & Prev _allergy_yes	0.830 (0.157, 0.966)	0.03
Work_construction & Age_<30	0.807 (-0.452, 0.979)	0.151
Work_construction & BMI_30+	0.904 (0.257, 0.988)	0.025
Work_chemicals & OSD	0.938 (0.279, 0.995)	0.026
Work_hairdressing & Age_30-49	0.840 (-0.617, 0.990)	0.198
Work_hairdressing & BMI_25-29	0.961 (-0.212, 0.999)	0.068
Work_food & Episodes_<5	0.873 (-0.565, 0.993)	0.162
Work_food & Able_to_work	0.979 (0.845, 0.997)	<0.001
Work_food & Prev _allergy_no	0.818 (0.161, 0.961)	0.029
Work_food & PGA_mild	0.937 (0.651, 0.989)	0.002
Work_food & Preservatives_exp	0.875 (0.216, 0.980)	0.026
Work_metal & Male	0.990 (-1.000, 1.000)	1
Work_metal & Mechanical_stress_exp	0.867 (0.578, 0.958)	<0.001
Work_health & BMI_<25	0.852 (0.276, 0.970)	0.018
Work_health & Episodes_5+	0.779 (-0.910, 0.996)	0.45
Work_health & Gloves_exp	0.885 (0.115, 0.985)	0.038
Able_to_work & Sick_leave	0.928 (0.772, 0.977)	<0.001
Sick_leave & Work_cleaning	0.820 (0.407, 0.945)	0.005
Sick_leave & Feet	0.755 (-0.158, 0.950)	0.081
Sick_leave & DLQI_large	0.838 (0.266, 0.964)	0.018
Prev _allergy_no & Duration_<2	0.789 (0.036, 0.954)	0.045
Prev _allergy_yes & Allergic_contact_dermat	0.989 (0.940, 0.998)	<0.001
Interdigital & Vesicular_eczema	0.734 (0.193, 0.912)	0.019

Variables pair	Correlation (95% CI)*	P-value
Wrist & Palm	0.893 (-0.121, 0.990)	0.064
Wrist & Interdigital	0.792 (0.111, 0.951)	0.034
Wrist & PGA_almost_clear	0.973 (-0.275, 0.999)	0.072
Forearms & Back_hand	0.917 (0.293, 0.990)	0.023
Forearms & Wrist	0.970 (0.643, 0.997)	0.006
Forearms & Pruritus_strong	0.758 (0.378, 0.906)	0.003
Atopic_hand_eczema & Pruritus_moderate	0.726 (-0.124, 0.934)	0.075
PGA_severe & Episodes_cont	0.865 (-0.088, 0.983)	0.061
PGA_mild & Pruritus_mild	0.805 (0.384, 0.938)	0.005
PGA_almost_clear & Duration_2-5	0.831 (-0.406, 0.983)	0.13
PGA_almost_clear & Work_chemicals	0.881 (0.463, 0.974)	0.006
PGA_almost_clear & Pruritus_no	0.938 (0.768, 0.983)	<0.001
Atopic_diathesis_yes & Atopic_hand_eczema	0.951 (0.821, 0.986)	<0.001
Wet_exp & Hyperkeratotic_eczema	0.704 (0.010, 0.912)	0.048
Detergents_exp & Work_food	0.871 (0.014, 0.983)	0.048
Detergents_exp & Wet_exp	0.925 (0.697, 0.982)	<0.001
Detergents_exp & Disinfectants_exp	0.968 (0.633, 0.997)	0.006
Detergents_exp & Solvents_exp	0.880 (0.022, 0.985)	0.048
Disinfectants_exp & Work_health	0.933 (0.764, 0.981)	<0.001
Lubri-refrigerants_exp & Age_50+	0.807 (-0.609, 0.985)	0.212
Solvents_exp & Duration_6+	0.782 (0.010, 0.952)	0.048
Solvents_exp & Lubri-refrigerants_exp	0.912 (0.736, 0.971)	<0.001
Solvents_exp & Industrial_oils_exp	0.906 (0.199, 0.989)	0.031
Industrial_oils_exp & Work_metal	0.934 (0.802, 0.978)	<0.001
Preservatives_exp & Irritant_contact_dermat	0.777 (-0.442, 0.972)	0.158

CI: confidence interval

* Correlation and its 95% CI are normalized in the interval [-1, 1]

Supplementary Table S5 - Normalized correlation between variables as shown in Supplementary Figure S2

Variables pair	Correlation (95% CI)*	P-value
Female & Work_hairdressing	0.757 (0.290, 0.917)	0.01
Female & Work_cleaning	0.728 (0.264, 0.900)	0.01
Male & BMI_25-29	0.482 (0.281, 0.626)	<0.001
Male & Work_construction	0.957 (0.808, 0.991)	<0.001
Age_<30 & Duration_2-5	0.414 (0.173, 0.584)	0.002
Age_<30 & BMI_<25	0.733 (0.620, 0.813)	<0.001
Age_<30 & Prev _allergy_no	0.557 (0.349, 0.699)	<0.001
Age_<30 & Wrist	0.495 (0.204, 0.679)	0.003
BMI_30+ & Age_50+	0.505 (0.315, 0.643)	<0.001
OSD & Job_loss-change	0.879 (0.766, 0.937)	<0.001
Work_construction & Pruritus_moderate	0.408 (-0.531, 0.835)	0.423
Work_chemicals & Palm	0.610 (-0.216, 0.881)	0.119
Work_chemicals & DLQI_moderate	0.363 (-0.167, 0.662)	0.163
Work_hairdressing & Age_<30	0.698 (0.403, 0.847)	<0.001
Work_hairdressing & Interdigital	0.666 (0.103, 0.875)	0.03
Work_hairdressing & Atopic_diathesis_no	0.570 (0.053, 0.804)	0.036
Work_hairdressing & Wet_exp	0.990 (-1.000, 1.000)	1
Work_hairdressing & Preservatives_exp	0.686 (0.297, 0.860)	0.005
Work_hairdressing & Gloves_exp	0.867 (0.342, 0.973)	0.013
Work_metal & Age_30-49	0.422 (0.087, 0.635)	0.019
Work_metal & Sick_leave	0.604 (0.331, 0.766)	<0.001
Work_metal & Pruritus_no	0.636 (0.365, 0.792)	<0.001
Work_metal & Mechanical_stress_exp	0.724 (0.507, 0.845)	<0.001
Able_to_work & BMI_30+	0.514 (0.296, 0.665)	<0.001
Sick_leave & Duration_<2	0.620 (0.470, 0.727)	<0.001
Sick_leave & Able_to_work	0.741 (0.646, 0.811)	<0.001
Job_loss-change & Duration_6+	0.647 (0.364, 0.804)	<0.001
Job_loss-change & PGA_severe	0.586 (0.026, 0.824)	0.043
Prev _allergy_yes & Allergic_contact_dermat	0.938 (0.902, 0.961)	<0.001
Wrist & Forearms	0.929 (0.886, 0.956)	<0.001
Forearms & Back_hand	0.597 (0.351, 0.749)	<0.001
Pruritus_no & PGA_almost_clear	0.723 (0.561, 0.825)	<0.001
Pruritus_mild & PGA_moderate	0.467 (0.306, 0.591)	<0.001
Vesicular_eczema & Episodes_5+	0.495 (0.234, 0.667)	0.001
Hyperkeratotic_eczema & Feet	0.487 (0.258, 0.645)	<0.001

Variables pair	Correlation (95% CI)*	P-value
Hyperkeratotic_eczema & Fingertip_dermat	0.570 (0.034, 0.808)	0.041
Fingertip_dermat & Irritant_contact_dermat	0.565 (0.254, 0.746)	0.003
Fingertip_dermat & Vesicular_eczema	0.610 (0.294, 0.785)	0.002
PGA_severe & Pruritus_strong	0.704 (0.585, 0.789)	<0.001
PGA_severe & Hyperkeratotic_eczema	0.588 (0.261, 0.771)	0.003
PGA_severe & DLQI_large	0.595 (0.441, 0.707)	<0.001
PGA_mild & Episodes_cont	0.371 (0.124, 0.549)	0.006
PGA_almost_clear & Episodes_<5	0.485 (0.159, 0.685)	0.008
PGA_almost_clear & DLQI_no-small	0.719 (0.572, 0.815)	<0.001
Atopic_diathesis_no & Pruritus_mild	0.375 (0.145, 0.543)	0.003
Atopic_diathesis_yes & Atopic_hand_eczema	0.858 (0.804, 0.897)	<0.001
Wet_exp & Detergents_exp	0.872 (0.819, 0.909)	<0.001
Detergents_exp & Disinfectants_exp	0.820 (0.689, 0.896)	<0.001
Detergents_exp & Solvents_exp	0.640 (0.410, 0.780)	<0.001
Disinfectants_exp & Work_food	0.779 (0.605, 0.876)	<0.001
Disinfectants_exp & Work_health	0.990 (0.976, 0.996)	<0.001
Lubri-refrigerants_exp & Work_metal	0.936 (0.881, 0.966)	<0.001
Lubri-refrigerants_exp & Prev _allergy_yes	0.598 (0.285, 0.774)	0.002
Solvents_exp & Work_chemicals	0.838 (0.646, 0.926)	<0.001
Solvents_exp & Industrial_oils_exp	0.887 (0.807, 0.933)	<0.001
Industrial_oils_exp & Male	0.830 (0.698, 0.904)	<0.001
Industrial_oils_exp & OSD	0.676 (0.438, 0.813)	<0.001
Industrial_oils_exp & Lubri-refrigerants_exp	0.958 (0.903, 0.982)	<0.001
Preservatives_exp & Atopic_diathesis_yes	0.596 (0.384, 0.736)	<0.001
DLQI_no-small & PGA_mild	0.521 (0.344, 0.650)	<0.001

CI: confidence interval

* Correlation and its 95% CI are normalized in the interval [-1, 1]

Supplementary Table S6 - Normalized correlation between variables as shown in Supplementary Figure S3

Variables pair	Correlation (95% CI)*	P-value
Work_construction & Irritant_contact_dermat	0.515 (-0.526, 0.888)	0.335
Work_chemicals & Cortic_systemic	0.722 (-0.410, 0.954)	0.165
Work_hairdressing & Cortic_mild-mod	0.872 (-0.712, 0.995)	0.222
Work_metal & Urea	0.672 (-0.177, 0.911)	0.095
Work_health & Atopic_hand_eczema	0.772 (0.250, 0.931)	0.015
Irritant_contact_dermat & Work_food	0.701 (0.005, 0.910)	0.049
Irritant_contact_dermat & Work_cleaning	0.766 (-0.055, 0.948)	0.059
Irritant_contact_dermat & Allergic_contact_dermat	0.662 (0.199, 0.857)	0.014
Allergic_contact_dermat & Work_chemicals	0.761 (0.124, 0.935)	0.031
Allergic_contact_dermat & Work_hairdressing	0.682 (-0.763, 0.976)	0.385
Hyperkeratotic_eczema & Fingertip_dermat	0.615 (-0.389, 0.909)	0.196
Cortic_potent & Work_metal	0.773 (-0.168, 0.957)	0.081
Cortic_potent & Calcineurin_inhibitors	0.713 (0.252, 0.890)	0.011
Cortic_potent & PUVA-UV_therapies	0.759 (0.065, 0.938)	0.04
Cortic_very_potent & Hyperkeratotic_eczema	0.761 (0.454, 0.896)	<0.001
Calcineurin_inhibitors & Alitretinoin	0.742 (0.343, 0.899)	0.004
PUVA-UV_therapies & Salicylic_acid	0.843 (0.620, 0.935)	<0.001
Cortic_systemic & Work_health	0.750 (0.004, 0.937)	0.049
Cortic_systemic & Vesicular_eczema	0.794 (0.270, 0.942)	0.014
Cortic_systemic & Cortic_potent	0.856 (-0.177, 0.983)	0.075
Cortic_systemic & Cortic_very_potent	0.932 (0.703, 0.984)	<0.001

CI: confidence interval

* Correlation and its 95% CI are normalized in the interval [-1, 1]

Supplementary Table S7 - Normalized correlation between variables as shown in Supplementary Figure S4

Variables pair	Correlation (95% CI)*	P-value
Work_construction & Allergic_contact_dermat	0.482 (0.050, 0.717)	0.034
Work_health & Atopic_hand_eczema	0.425 (0.207, 0.583)	<0.001
Work_cleaning & Cortic_mild-mod	0.590 (0.222, 0.785)	0.006
Irritant_contact_dermat & Work_food	0.342 (0.023, 0.556)	0.038
Irritant_contact_dermat & Work_metal	0.333 (0.063, 0.525)	0.02
Irritant_contact_dermat & Work_health	0.546 (0.372, 0.671)	<0.001
Allergic_contact_dermat & Work_hairdressing	0.549 (0.218, 0.740)	0.005
Allergic_contact_dermat & Fingertip_dermat	0.449 (0.069, 0.674)	0.026
Hyperkeratotic_eczema & Salicylic_acid	0.671 (0.437, 0.808)	<0.001
Fingertip_dermat & Irritant_contact_dermat	0.541 (0.249, 0.720)	0.002
Fingertip_dermat & Vesicular_eczema	0.613 (0.318, 0.780)	0.001
Fingertip_dermat & Hyperkeratotic_eczema	0.625 (0.167, 0.831)	0.016
Cortic_mild-mod & Urea	0.529 (0.398, 0.632)	<0.001
Cortic_potent & Work_cleaning	0.619 (0.255, 0.805)	0.005
Cortic_very_potent & Cortic_systemic	0.508 (0.303, 0.652)	<0.001
Salicylic_acid & Work_chemicals	0.432 (-0.152, 0.726)	0.129
Salicylic_acid & Cortic_potent	0.505 (0.284, 0.658)	<0.001
Salicylic_acid & Cortic_very_potent	0.511 (0.321, 0.648)	<0.001
Salicylic_acid & PUVA-UV_therapies	0.560 (0.389, 0.682)	<0.001
Salicylic_acid & Alitretinoin	0.482 (0.256, 0.639)	<0.001
PUVA-UV_therapies & Calcineurin_inhibitors	0.490 (0.329, 0.612)	<0.001

CI: confidence interval

* Correlation and its 95% CI are normalized in the interval [-1, 1]